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Major depressive disorder subtypes and depression symptoms in multiple sclerosis: What is different compared to the general population?

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ABSTRACT

Objective: To compare and characterize major depressive disorder (MDD) subtypes (i.e., pure atypical, pure melancholic and mixed atypical-melancholic) and depression symptoms in persons with multiple sclerosis (PwMS) with persons without MS (Pw/oMS) fulfilling the DSM-5 criteria for a past 12-month MDD.

Methods: MDD in PwMS ($n = 92$) from the Swiss Multiple Sclerosis Registry was compared with Pw/oMS ($n = 277$) from a Swiss community-based study. Epidemiological MDD diagnoses were based on the Mini-SPIKE (shortened form of the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology). Logistic and multinomial regression analyses (adjusted for sex, age, civil status, depression and severity) were computed for comparisons and characterization. Latent class analysis (LCA) was conducted to empirically identify depression subtypes in PwMS.

Results: PwMS had a higher risk for the mixed atypical-melancholic MDD subtype (OR = 2.22, 95% CI = 1.03–4.80) compared to Pw/oMS. MDD in PwMS was specifically characterized by a higher risk of the two somatic atypical depression symptoms 'weight gain' (OR = 6.91, 95% CI = 2.20–21.70) and 'leaden paralysis' (OR = 3.03, 95% CI = 1.35–6.82) and the symptom 'irritable/angry' (OR = 3.18, 95% CI = 1.08–9.39).

Conclusions: MDD in PwMS was characterized by a higher risk for specific somatic atypical depression symptoms and the mixed atypical-melancholic MDD subtype. The pure atypical MDD subtype, however, did not differentiate between PwMS and Pw/oMS. Given the high phenomenological overlap with MS symptoms, the mixed atypical-melancholic MDD subtype represents a particular diagnostic challenge.

Abbreviations: MDD, Major Depressive Disorder.

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1. Introduction

Empirical evidence demonstrates that major depressive disorder (MDD) is the most prevalent comorbidity of the immune-mediated, inflammatory disease multiple sclerosis (MS) [1]. Compared to the lifetime prevalence of MDD ranging between 12.8% to 17.1% in the general community [2–4], prevalence was reported substantially higher in persons with MS (PwMS), with the magnitude of difference depending on the examined sample (clinical, community/registry-based) and the choice of instrument [5,6]: while studies using dimensional screening tools with different cut-offs led to lifetime prevalence ranges between 20 and 50% [e.g., 7, 8–11], studies applying clinical diagnostic interviews showed ranges between 17 and 34% [11–13] together with a 12-month prevalence of 15.7% [9]. The burden and the consequences of comorbid MDD are high and constitute one of the main determinants of decreased quality of life in PwMS [14–17]. Thus, the issue of MDD in MS still demands more attention in research and clinical practice [18].

MDD is a well-treatable mental disorder [19,20]. However, MDD in PwMS is mostly not adequately recognized and hence undertreated [18]. The high symptom overlap between MDD and MS represents a particular diagnostic challenge and may result in potential distortions of MDD prevalence in PwMS [5]. For example, fatigue is one of the most common symptoms in MS and, at the same time, represents a major diagnostic criterion for MDD, and also psychomotoric retardation and sleeping problems occur in both MDD and MS [5]. Furthermore, the diagnostic process is hampered by the fact that both MDD and MS bear a high symptom heterogeneity. Therefore, apart from the comparison of depression symptoms, focusing on homogeneous subtypes (i.e., specified clusters of differing symptoms) is a promising approach to achieve more tailored diagnostics and treatments [21].

Studies directly comparing depression symptoms between PwMS and persons without MS (Pw/oMS) are still scarce: some studies found that MDD in PwMS was characterized by a higher occurrence of either neurovegetative or somatic symptoms or health-related concerns and suicidal ideation [22–26], whereas other studies, statistically controlling for depression severity, concluded that the presentation of depression symptoms is highly similar [27,28]. Certain non-somatic depression symptoms, such as future pessimism, were also judged to be relevant in PwMS [25,29], but these findings were not consistently replicated. Apart from the diagnostic threshold level of MDD, the subsyndromal symptom 'irritability' hallmarking affective instability was also emphasized within PwMS [12,30].

Evidence is even scarcer regarding depression subtypes. The most consistent finding concerns a distinction between melancholic and atypical symptom constellations [21,31]; these two depression subtypes are also catalogued as MDD specifiers in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [32]. The melancholic MDD subtype (MDD episode characterized by: a) either loss of pleasure or lack of reactivity, and b) three or more of the following features: distinct quality of depressed mood, worse in the morning, early morning awakening, psychomotor retardation or agitation, anorexia or weight loss, excessive guilt) shows a lifetime prevalence of 24–32% [33–35] and cumulative incidence rates of 7% [33], the atypical MDD subtype (MDD episode characterized by: a) mood reactivity, and b) two or more of the following features: weight gain or increase in appetite, hypersomnia, leaden paralysis, long-standing pattern of interpersonal rejection sensitivity) between 15 and 39% [36–38] and 4% [33], respectively. Notably, atypical depression, which is correlated with inflammatory processes [39–41] and might particularly benefit from specific treatments [41,42], deserves further examination in PwMS. The only study so far [29] compared sum scores of atypical and melancholic depression symptom clusters between PwMS and Pw/oMS, without finding any differences. A potential problem with such clustering algorithms is the overlap in some depressive symptomatology between the atypical and melancholic clusters [43]. Consequently, they are not defined in their distinct, pure forms, as required by the DSM-criteria. Apart from pure melancholic and atypical MDD subtypes, however, melancholic and atypical depression subtypes have indeed shown substantial longitudinal overlap in nearly half of all cases, particularly in women [33,34,44,45]. In fact, such defined mixed atypical-melancholic MDD subtypes (i.e., persons fulfilling specifiers criteria for both atypical and melancholic depression) have not been considered in DSM-classifications so far. Because women represent the majority of PwMS in most developed countries, the mixed atypical-melancholic MDD subtype may also be more prevalent in the population of PwMS and thus requires further examination.

Therefore, the aims of the current study were: 1) to compare depression symptoms between PwMS and Pw/oMS; 2) to compare MDD subtypes between PwMS and Pw/oMS with a MDD subtype definition based on a) distinct pure atypical, pure melancholic, and mixed atypical-melancholic MDD subtypes according to DSM-5 criteria [32] and b) MDD subtypes based on latent class analysis (LCA), a data-driven approach; and 3) to describe these MDD subtypes by depression characteristics and MS characteristics in PwMS. In particular, a more frequent occurrence of the atypical MDD subtype / atypical depression symptoms in PwMS compared to Pw/oMS was hypothesized, given that inflammatory processes play a central role in MS and are thought to be involved in atypical depression [39–41]. We also expected that the mixed atypical-melancholic MDD subtype showing a female preponderance was relevant in PwMS [33,34,44]. Finally, by applying LCA we expected that the atypical, melancholic, and mixed atypical-melancholic MDD subtypes would be replicated while retaining the option to detect potentially novel MDD subgroups that could be related to MS.

2. Materials and methods

2.1. Study sample

Data were derived from two sources: a) the Swiss Multiple Sclerosis Registry (SMSR), and b) the epidemiology survey of the ZInEP project (Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie, i.e. the „Zurich Program for Sustainable Development of Mental Health Services"):

a) The SMSR is an ongoing, prospective, longitudinal observational study focusing on the life circumstances of adult PwMS and their relatives and proxies in Switzerland (n = 2370; status quo: August 31, 2020) (http://www.Clinical- Trials.gov identifier: NCT02980640). This study was initiated and is funded by the Swiss MS Society. The patient-centered SMSR is based on a citizen-science approach directly involving PwMS in central functions. Details on the study design and evidence of the representativeness of the SMSR for the Swiss MS population are described elsewhere [46–48]. For the current study, the 12 month post baseline survey data containing a focus topic depression (n = 567) was considered. The SMSR was approved by the Ethics Committee Zurich (PB-2016-00894) and written informed consent was obtained from all participants [46].

b) The ZInEP epidemiology survey was established in order to generate comprehensive data about mental health in the general population of adults in the canton of Zurich [49]. This survey was designed as a cross-sectional sequel to the longitudinal Zurich Study [50], i.e., age and sex structure and instruments were parallelized. It consisted of three components: a) a brief telephone screening (n = 9829), b) a structured face-to-face-interview of a sample stratified along sex, age and mental psychiatric symptoms severity (n = 1500) supplemented by self-report questionnaires, and c) a longitudinal survey (n = 227) [49]. For the present study, information from the face-to-face-interview (n = 1500) was used.

All subjects with an epidemiological MDD diagnosis at any time in the past 12 months minimum were selected from the SMSR (n = 92) and

the ZInEP survey (n = 277), leading to an overall sample of 369 depressed persons. Exclusion criterion was a MS diagnosis in the ZInEP survey, not occurring in any participant. In contrast, 4 participants were excluded in the SMSR sample, as they did not fulfill the required past 12 months time-frame of MDD. The detailed composition of the samples used for subsequent data analysis is depicted in a flow-chart (Fig. 1).

2.2. Measurements

2.2.1. Socio-demographic characteristics

The socio-demographic variables sex, age, education, urbanicity, nationality and civil status were drawn from the SMSR baseline assessment and from the ZInEP screening interview, respectively.

2.2.2. Depression assessment

The instruments assessing depression were parallelized between the SMSR and the ZInEP survey by using the Mini-SPIKE, a shortened version of the SPIKE (Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbance for Epidemiology – Version 10). This face-to-face-interview, based on the DSM criteria, was originally developed within the scope of the Zurich Study [50,51]. It covers most psychopathological subthreshold and threshold syndromes / disorders for the time span of the last 12 months and showed very high validity and inter-rater reliability [49]. This instrument was found to have high sensitivity and modest specificity (0.95 and 0.59, respectively) for MDD [50]. In the SMSR, the Mini-SPIKE was implemented as a self-assessment and additional information was assessed to also cover the time span before the last 12 months.

DSM-5 criteria [32] derived from the Mini-SPIKE were applied to establish an epidemiological MDD diagnosis. Depression severity was computed by the MDD diagnosis criteria sum score ranging from 5 to 9 symptoms. The atypical and melancholic MDD specifiers were separated into a) pure subtypes, and b) mixed subtypes if a person fulfilled both atypical and melancholic MDD specifiers criteria (excluding the unequivocal specifier criterion 'mood reactivity').

On the symptom level, all DSM-5 MDD classification criteria, supplemented by non-covered symptoms of the atypical MDD and melancholic MDD specifiers, were considered (for a full list, see "Depression symptoms.docx" in Supplementary material). The neurovegetative MDD criteria were disaggregated as this approach turned out to be beneficial in detecting depression subtypes in previous studies [52]. 'Significant weight gain / loss' was fulfilled if the self-reported weight change within one month reached at least 5% of the initial body weight. Finally, the symptom 'irritable/angry' was added as it was judged to be relevant within the assessment of MDD in PwMS [12].

In the SMSR, the 7-item Beck Depression Inventory-Fast Screen (BDI-FS) [53] was also applied. This self-rating questionnaire assessing current subjective burden resulting from depression (time-span: past two weeks) has been specifically validated for use in PwMS [54]. The BDI-FS counteracts the potentially biased overestimation of MDD prevalence in PwMS as it captures depression under exclusion of somatic (that is, MS-overlapping and therefore likely confounding) features. Clinically significant depressive symptomatology was defined as a BDI-FS sum score greater than or equal to 4 as this cut-off showed sensitivity between 0.97 and 1.00 and specificity between 0.79 and 0.99 [55,56].

A visual analogue scale (VAS) ranging from 0 (no burden at all) to 100 (maximal burden) was available from the Mini-SPIKE for both surveys, and analyzed both metric and dichotomized by high burden (larger than or equal to 75) versus low burden (lower than 75).

Information on additional clinical and health-related characteristics of depression and MS can been found in the Supplementary material (see "Clinical and health-related characteristics.docx").

2.3. Statistical analysis

The analysis design comprised two steps: In the first step, the pure and mixed MDD subtypes and depression symptoms based on DSM-5 definitions were compared in the overall sample of depressed PwMS and Pw/oMS by regression analysis. These regression analyses were adjusted for confounders – both theoretically and empirically derived ones. In the second step, LCAs on 19 depression symptoms and a variable assessing subjective burden were applied. Latent class characterization was based on odds ratios (ORs) with 95% confidence intervals (CI) from multivariate multinomial logistic regressions and performed based on both the overall sample and restricted only to PwMS. Further details of these steps are described in the Supplementary material (see "Regression

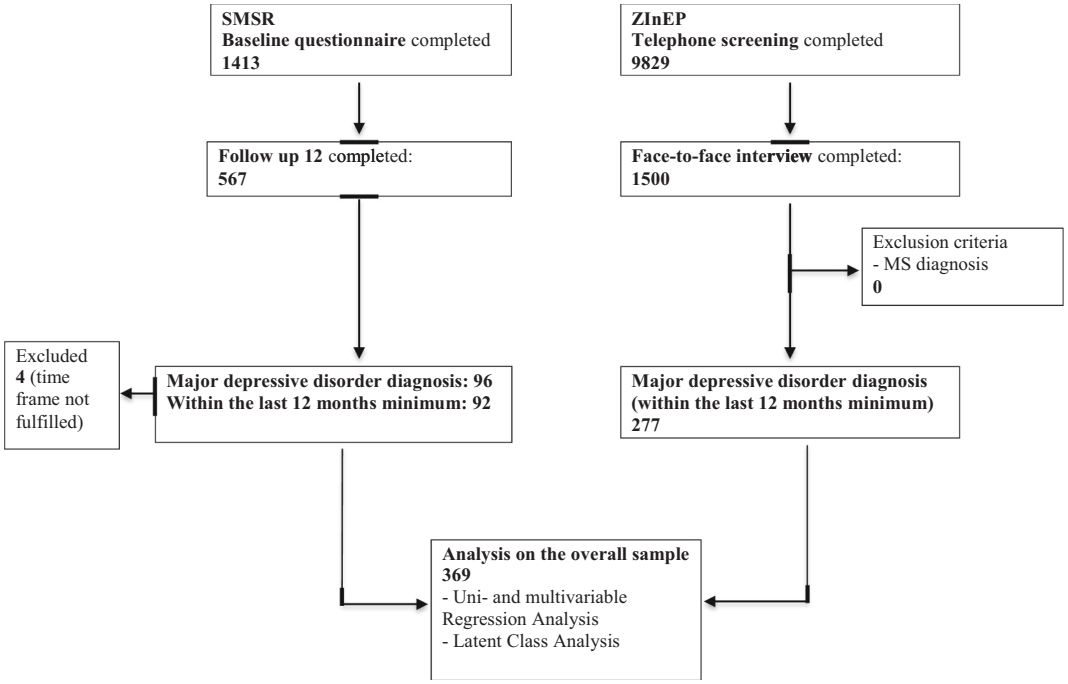

Fig. 1. Flow chart describing the study samples of the Swiss Multiple Sclerosis Registry and the ZInEP epidemiology survey (numbers reflect numbers of persons).

analysis and latent class analysis.docx"). Additional sensitivity analysis was performed with the variables antidepressant or psychotherapy treatment (overall), and DMT (PwMS) due to their potential effect on MDD presentation. In descriptive and regression analyses, we took into account the stratification of the ZInEP sample.

Descriptive analysis and regression models were performed using the IBM SPSS Statistics for Macintosh, version 25.0 [57] and Stata software for Macintosh, version 13.1 [58]. SAS Version 9.4 was used in analyses accounting for the stratification of the ZInEP sample. LCA was conducted using Mplus for Macintosh, version 8 [59]. Statistical significance was defined as a p-value <0.05.

3. Results

3.1. Descriptive statistics

The comparisons between depressed PwMS and Pw/oMS concerning socio-demographics are presented in Table 1. The groups were socio-demographically comparable apart from the following significantly differing characteristics: the sample of depressed PwMS encompassed more women (80.4% vs. 58.2%) and, moreover, a higher age compared with Pw/oMS (median: 49.0 vs. 29.0). Additionally, PwMS were more frequently married or in a registered partnership (47.3% vs. 25.4%). Consequently, the socio-demographic variables sex, age and civil status were considered confounding variables, in additional to the theoretical-derived confounding variable depression severity, in all subsequent regression analyses on PwMS versus Pw/oMS (see Tables 3 and 5).

The past 12-month prevalence rate of MDD was higher in PwMS (n = 92; 16.2%) compared to Pw/oMS (n = 277; 11.6%, weighted) showing the following proportions for PwMS / Pw/oMS: OR = 1.5 (95% CI = 1.1–2.0; unadjusted), and OR = 1.2 (95% CI = 0.9–1.7; adjusted for sex and age) (data not tabulated).

Table 1
Socio-demographic characteristics of persons with MS (PwMS) and persons without MS (Pw/oMS) fulfilling the criteria for a 12-month MDD diagnosis.

	PwMS (n = 92)	**Pw/oMS** (n = 277)
Socio-demographics		
Sex		
Men	18 (19.6%)	122 (41.8%[a])
Women	74 (80.4%)	155 (58.2%[a])
Age, years	49.0 (42.0;56.8)	29.0 (24.0;36.0[a])
	range: 23–81	range: 21–42
Education[b]		
low	48 (53.9%)	136 (51.1%[a])
high	41 (46.1%)	141 (48.9%[a])
	1	
Urbanicity[c]		
Urban	52 (56.5%)	165 (55.5%[a])
Rural	40 (43.5%)	112 (44.5%[a])
Nationality		
Swiss	86 (93.5%)	258 (90.4%[a])
Other	6 (6.5%)	19 (9.6%[a])
Civil status		
Married, registered partnership	43 (47.3%)	57 (25.4%[a])
Other	48 (52.7%)	220 (74.6%[a])
	2	

Results are shown as numbers (percentage), or medians (interquartile range (25PI;75PI)).
Pw/oMS: Zurich (more than 400′000 residents) and Winterthur (more than 100′000 residents) were considered as urban areas, all other communities as rural areas.
[1]*n=3 missing;*[2]*n=1 missing*
Abbreviations: MDD = Major Depressive Disorder; PwMS = Persons with Multiple Sclerosis; Pw/oMS = Persons without Multiple Sclerosis.
[a] weighted relative percentage according to ZInEP stratification.
[b] High: High school or higher corresponding to 12–13 years of education.
[c] PwMS: based on the Federal Statistical Office of Switzerland; areas classified as 'urban to rural' were defined as rural.

MDD subtypes, and MDD- and somatic characteristics are shown in Table 2. The pure atypical and melancholic MDD subtypes according to DSM-5 were similarly distributed between PwMS and Pw/oMS. The sum scores of the melancholic and atypical specifier criteria and of the overall depression symptoms, respectively, were also comparatively distributed. However, the mixed atypical-melancholic MDD subtype was significantly higher in PwMS (n = 46; 50%) than in Pw/oMS (n = 122; 35.1%, weighted). The Body Mass Index (BMI) also significantly differed between the samples with PwMS showing a higher BMI in comparison with Pw/oMS. In contrast, antidepressant and psychotherapeutic treatment and the subjective burden resulting from depression did not differ between PwMS and Pw/oMS. Finally, information on the temporal order

Table 2
MDD subtypes, MDD characteristics and somatic characteristics of persons with MS (PwMS) and persons without MS (Pw/oMS) fulfilling the criteria of a 12-month MDD diagnosis.

	PwMS (n = 92)	**Pw/oMS** (n = 277)
MDD subtypes (DSM-5 criteria)		
12-month prevalence		
Pure atypical	4 (4.3%)	21 (8.4%[a])
Pure melancholic	21 (22.8%)	62 (27.5%[a])
Mixed atypical-melancholic	46 (50.0%)	122 (35.1%[a])
Not assignable	21 (22.8%)	72 (29.0%[a])
Sum of melancholic specifier criteria	3.0 (2.0;4.0)	3.0 (2.0;4.0[a])
Sum of atypical specifier criteria	2.0 (1.0;3.0)	1.5 (1.0;2.0[a])
MDD characteristics		
Subjective burden resulting from depression		
0–100	80.0 (70.0;90.0)	80.0 (60.0;90.0[a])
	1	
Sum score of depressive symptoms		
5 to 9	7.0 (6.3;8.0)	7.0 (6.0;8.0[a])
Treatment		
Antidepressants		
yes	24 (26.1%)	92 (33.0%[a])
no	68 (73.9%)	185 (67.0%[a])
Psychotherapy		
yes	34 (37.0%)	102 (28.7%[a])
no	58 (63.0%)	175 (71.3%[a])
Antidepressants or Psychotherapy		
yes	45 (48.9%)	126 (42.0%[a])
no	47 (51.1%)	151 (58.0%[a])
Somatic characteristic		
Body Mass Index	25 (22.0;28.9)	23 (20.7;25.3[a])
	2	*3*
Additional depression characteristics		
Only available for PwMS		
BDI-FS		
Clinically relevant depressive symptomatology	53 (57.6%)	N/A
	4	
Temporal order of depression with MS diagnosis		N/A
Before	4 (4.7%)	
After	46 (54.1%)	
At the same time	6 (7.1%)	
Both before and after	29 (34.1%)	
	5	
WHO-Five Well-being index		N/A
Sum score	12 (9.0;16.0)	
Good well-being	40 (46.0%)	
Poor well-being, indication for testing MDD given	47 (54.0%)	
	6	

Results are shown as numbers (percentage), or medians (interquartile range (25PI;75PI)).
[1]*n=3 missing;*[2]*n=3 miss;*[3]*n=2 miss;*[4]*n=6 missing;*[5]*n=7 miss;*[6]*n=5 miss*
NA = not applicable.
Abbreviations: PwMS = Persons with Multiple Sclerosis; Pw/oMS = Persons without Multiple Sclerosis; MDD = Major Depressive Disorder; BDI-FS = Beck Depression Inventory-Fast Screen for Medical Patients; WHO = World Health Organization.
[a] Weighted relative percentage according to ZInEP stratification.

of depression and MS, BDI-FS scores and the WHO-Five Well-being index was only available for PwMS: 58% of the group of PwMS reached the threshold for clinically relevant depressive symptomatology; more than half (54%) of the PwMS confirmed that the depression occurred after the MS diagnosis, while around one third responded that the depression occurred both before and after the MS diagnosis; and 54% of the PwMS had a poor well-being (Table 2).

The MS characteristics (such as MS form, time since MS diagnosis, disease modifying therapies (DMT), current relapses, EDSS proxy measure, MS symptoms and mobility) and health-related quality of life of depressed PwMS compared to non-depressed PwMS are depicted in the Supplementary material (see "Table 1. docx"). Depressed PwMS reported a significantly lower health-related quality of life and a significantly higher frequency of symptoms with a substantial individual burden such as fatigue or weakness.

3.2. MDD subtypes and depression symptoms based on DSM-5

Table 3 displays the unadjusted and adjusted ORs with 95% CI from the univariable and multivariable logistic regression analyses focusing on pure and mixed MDD subtypes and depression symptoms according to DSM-5. The risk for PwMS to fulfill the criteria for the mixed atypical-melancholic MDD subtype was around twofold higher in comparison to Pw/oMS.

Regarding specific depression symptoms, the PwMS depicted a higher risk for the depression symptoms 'weight gain' being 'irritable, angry', and 'leaden paralysis' (i.e., heavy, leaden feelings in arms or legs) after adjustment. The depression symptoms 'weight gain' and 'leaden paralysis' associated with PwMS represent somatic atypical MDD subtype criteria, however, the full set of criteria (pure atypical MDD subtype) did not significantly differ between the samples (Table 3).

These results also remained stable even after additional adjustment for the not significantly differing sociodemographic variables education, urbanicity, and nationality, and antidepressant or psychotherapy treatment (overall), as well as DMT (PwMS) (data not shown).

The higher risk for 'psychomotor retardation', 'early-morning awakening', 'worse in the morning', 'taedium vitae, suicidal thoughts/attempt', and 'no mood reactivity' in PwMS was no longer significant after adjustment (Table 3).

Table 3
Odds ratios and confidence intervals (95%) from univariable and multivariable logistic regressions for the overall MDD sample ($n = 369$) depicting the risk of persons with MS (PwMS) versus persons without MS (Pw/oMS) to show a specific MDD subtype and depression symptom.

	PwMS versus Pw/oMS (weighted) (ref.)	**PwMS versus Pw/oMS (weighted) (ref.)**
	Unadjusted	Adjusted for sex, age, depression severity and civil status
MDD subtypes (DSM-5 criteria)		
12-month prevalence		
Pure atypical	0.55 (0.15–1.59)	0.97 (0.30–3.10) [a]
Pure melancholic	0.78 (0.42–1.44)	0.48 (0.17–1.38) [a]
Mixed atypical melancholic	**1.85 (1.12–3.03)**	**2.22 (1.03–4.80)**[a]
Depression symptoms		
Depressed mood	1.01 (0.37–2.72)	1.15 (0.11–11.63)
Anhedonia, loss of interest/activity	5.07 (0.59–43.52)	2.27 (0.19–27.04)
Fatigue, loss of energy	0.93 (0.37–2.40)	0.65 (0.07–1.37)
Psychomotor retardation	**2.48 (1.48–4.17)**	1.29 (0.68–2.44)
Psychomotor agitation	0.86 (0.50–1.49)	1.21 (0.49–2.95)
Early-morning awakening	**2.41 (1.43–4.07)**	1.42 (0.62–3.26)
Worse in the morning	**1.76 (1.02–3.04)**	1.58 (0.65–3.85)
Hypersomnia	0.82 (0.49–1.41)	1.12 (0.46–2.72)
Weight loss	0.61 (0.23–1.66)	0.57 (0.14–2.29)
Weight gain	**3.95 (1.37–11.65)**	**6.91 (2.20–21.70)**
Loss of appetite	0.71 (0.42–1.21)	0.52 (0.22–1.24)
Increased appetite	1.43 (0.83–2.46)	2.17 (0.90–5.22)
Irritable, angry	1.55 (0.87–2.76)	**3.18 (1.08–9.39)**
Hypersensitivity to critical remarks	0.66 (0.39–1.12)	0.48 (0.20–1.18)
Leaden paralysis	**4.09 (2.39–6.99)**	**3.03 (1.35–6.82)**
Feelings of inferiority, loss of self-confidence, guilt	0.89 (0.44–1.80)	0.42 (0.10–1.75)
Concentration/memory problems, difficulties in decision making	0.78 (0.34–1.78)	0.98 (0.25–3.88)
Taedium vitae, suicidal thoughts/attempt	**1.77 (1.08–2.93)**	1.02 (0.35–2.96)
No mood reactivity	**1.76 (1.08–2.89)**	1.43 (0.62–3.28)
Depression characteristic		
Subjective burden resulting from depression (0–100, cut-off ≥75)	1.21 (0.71–2.06)	1.45 (0.58–3.61)

Bold indicates significant Odds Ratios ($p < 0.05$).
Abbreviations: MDD = Major Depressive Disorder; ref.: reference.
[a] No adjustment for depression severity as number of symptoms is an inherent feature of the mixed and pure depression subtype diagnoses.

3.3. Depression subtypes derived by LCA

3.3.1. Selection of a LCA model

For the selection of a final LCA model, the statistical fit indices, the aspect of parsimony and the theoretical interpretability were taken into account. Based on the combination of optimal statistical fit indices and the aspect of parsimony, the two-, three-, and four class LCA models were chosen for further consideration (Table 4). For more insight into the theoretical interpretability, these LCA models were plotted (Figures not shown): in the two-class model, the two latent classes mainly differentiated between more and less severe depression. From the three-class model on, the hypothesized theoretical framework with atypical and melancholic depression profiles were discriminable. The four-class model, however, led to extreme and clinically not meaningful estimates (so called boundary estimates). Under consideration of all these statistical and theoretical aspects, the three-class model was therefore chosen and implemented in further analyses.

3.3.2. Labeling of the three latent classes

Fig. 2 depicts the selected three-class LCA model. The different colored plots show the estimated probabilities (y-axis: 0 to 1) of the three classes manifesting the corresponding depression symptom (x-axis). This thus provided class-specific depression symptom profiles on all depression symptoms. In other words, every class contained a group of persons with similar depression symptom profiles and the three plots represent the overall depression symptom profiles of classes one to three. In this three-class LCA model, two severe classes (class 1 (blue) and class 2 (red)) with high probabilities for most depression symptoms were distinguishable from the less severe class (class 3 (green)): The

Table 4
Model fit indices derived from unconditional latent class analysis with classes ranging from 1 to 5 based on the overall MDD sample (n = 369) including persons with MS (PwMS) ($n = 92$) and persons without MS (Pw/oMS) ($n = 277$).

Fit statistics	Class 1	Class 2	Class 3	Class 4	Class 5
AIC	7615.214	7473.845	7441.327	7416.552	7404.213
BIC	7693.429	7634.187	7683.797	7741.148	7810.936
ABIC	7629.977	7504.109	7487.092	7477.818	7480.980
Entropy	N/A	0.570	0.704	0.770	0.803
LMR-LRT, adj.	N/A	$p < 0.001$	$p = 0.1184$	$p = 0.1606$	$p = 0.4458$

NA, not applicable.
Abbreviations: MDD = Major Depressive Disorder; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ABIC = Sample-Size Adjusted Bayesian Information Criterion; LMR-LRT adj. = Lo-Mendell-Rubin likelihood ratio test, adjusted.

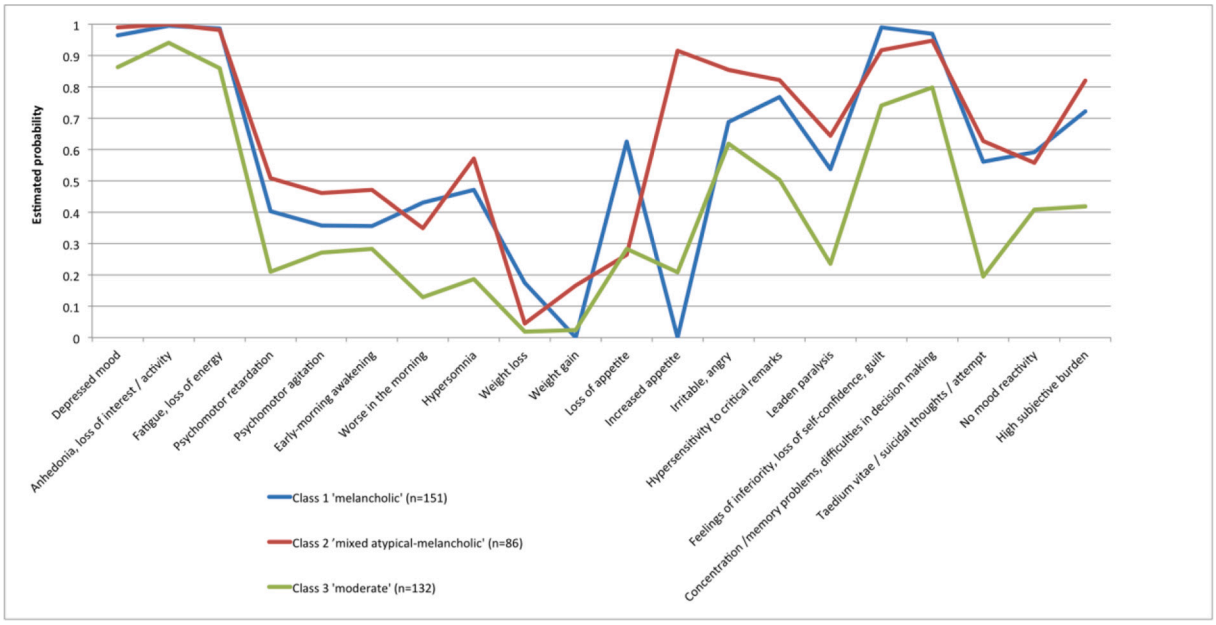

Fig. 2. Unconditional three-class model derived from latent class analysis on the overall MDD sample (n = 369).

estimated probabilities illustrate that the severe class 1 (n = 151) showed a predominantly melancholic depression symptom profile, therefore it was labeled 'melancholic'. In contrast, the severe class 2 (n = 86) included individuals with both high probabilities of atypical, i.e., reversed vegetative depression symptoms, and melancholic depression features. Due to its mixed symptom profile, this class was labeled 'mixed atypical-melancholic'. Finally, class 3 (n = 132) was labeled 'moderate' as its depression symptom profile was characterized by less severity, that is, lower probabilities for most depression symptoms.

Table 5
Odds ratios and confidence intervals (95%) from multivariable multinomial logistic regressions characterizing the empirically derived latent classes on the overall MDD sample (n = 369).

	Melancholic (n = 151) versus moderate (n = 132) (ref.)	**Mixed atypical-melancholic (n = 86) versus moderate (n = 132) (ref.)**
MS Diagnosis		
Persons with MS (PwMS)	1.74 (0.74–4.08)	**2.59 (1.01–6.64)**
Persons without MS (Pw/oMS)	*ref.*	*ref.*
Socio-demographics		
Sex		
Women	0.97 (0.58–1.61)	**1.93 (1.03–3.59)**
Men	*ref.*	*ref.*
Age	0.99 (0.96–1.02)	0.97 (0.94–1.01)
Civil status		
Other	1.63 (0.92–2.90)	1.76 (0.89–3.47)
Married, registered partnership	*ref.*	*ref.*
Depression characteristics		
Antidepressants or psychotherapy		
yes	**3.47 (2.09–5.77)**	**2.28 (1.27–4.09)**
no	*ref.*	*ref.*

Bold indicates significant Odds Ratios ($p < 0.05$).
Missing latent classes: melancholic: n = 1.
Abbreviations: MDD = Major Depressive Disorder; MS = Multiple Sclerosis; PwMS = Persons with Multiple Sclerosis; Pw/oMS = Persons without Multiple Sclerosis; ref.: reference.

3.3.3. *Overall: characterization of the three latent classes*

Relevant characteristics of the three latent classes of the overall sample of subjects with MDD are shown in Table 5. PwMS and women had a higher risk of belonging to the 'mixed atypical-melancholic' class. Both severe classes ('mixed atypical-melancholic' and 'melancholic') were additionally associated with more antidepressants or psychotherapy treatment in comparison to the moderate class. However, neither age nor civil status were significantly associated with one of the severe latent classes (Table 5).

3.3.4. *PwMS: characterization of the three latent classes*

Focusing only on PwMS, the 'melancholic' class but not the 'mixed atypical-melancholic' class was associated with a significantly higher risk for clinically relevant depressive symptomatology assessed by the BDI-FS compared to the 'moderate' class (Table 6). Both severe classes were associated with a high subjective burden resulting from depression. In contrast, female sex and antidepressant or psychotherapeutic treatment were not significantly associated with the 'melancholic' or the 'mixed atypical-melancholic' classes. Also with regard to the MS-related variables time since MS diagnosis, total number of relapses, and EDSS proxy measure, no significant associations characterizing the 'melancholic' or the 'mixed atypical-melancholic' class were found (Table 6).

4. Discussion

This nationwide Swiss MS registry study provides new important insight into MDD in PwMS by characterizing and comparing MDD subtypes and depression symptoms with a community-based sample of depressed Pw/oMS. We found that MDD in PwMS was characterized by a higher risk of somatic atypical depression symptoms, but not for the pure atypical MDD subtype. Moreover, we demonstrated for the first time that the mixed atypical-melancholic MDD subtype was linked to PwMS. This MDD subtype occurred in 50% of all PwMS and comprised a high overlap with MS-inherent disease characteristics, thus representing a particular challenge from a diagnostic point of view.

4.1. *MDD subtypes*

PwMS were more likely than Pw/oMS to develop the mixed atypical-melancholic MDD subtype (i.e., fulfilling the criteria for both the

Table 6
Odds ratios and confidence intervals (95%) from multivariable multinomial logistic regressions restricted to the sample of PwMS (n = 92) characterizing the empirically derived latent classes on the overall MDD sample (n = 369).

	Melancholic (*n* = 38) versus moderate (*n* = 29) (ref.)	Mixed atypical-melancholic (*n* = 25) versus moderate (n = 29) (ref.)
Socio-demographics		
Sex		
Women	4.43 (0.61–32.20)	2.83 (0.35–23.03)
Men	*ref.*	*ref.*
Depression characteristics		
BDI-FS		
Clinically relevant depressive symptomatology	**6.30 (1.42–27.91)**	3.08 (0.65–14.64)
Antidepressants or Psychotherapy		
yes	3.26 (0.74–14.35)	1.56 (0.32–7.48)
no		
Subjective burden resulting from depression		
0–100	**1.05 (1.00–1.11)**	**1.08 (1.02–1.14)**
MS characteristics		
Time since MS diagnosis	0.99 (0.92–1.07)	0.99 (0.91–1.08)
Relapses[a] *(total number, lifetime)*	0.96 (0.86–1.07)	0.95 (0.85–1.06)
EDSS proxy measure[b] *(cut-off: ≥ 4)*	0.63 (0.12–3.42)	0.62 (0.10–3.75)

Bold indicates significant Odds Ratios ($p < 0.05$).
Abbreviations: MDD = Major Depressive Disorder; BDI-FS = Beck Depression Inventory-Fast Screen for.
Medical Patients; PwMS = Persons with Multiple Sclerosis; EDSS = Expanded Disease Status Scale.
[a] Without n = 8 persons with PPMS.
[b] (Kaufmann et al., 2020) Kaufmann M, Salmen A, Barin L, et al. (2020) Development and validation of the self-reported disability status scale (SRDSS) to estimate EDSS-categories. *Mult Scler Relat Disord* 42: doi:https://doi.org/10.1016/j.msard.2020.102148.

atypical and the melancholic depression subtypes), which is in line with our hypothesis. This was not only shown by the subtyping of pure versus mixed DSM-5 criteria, but also successfully replicated by the data-driven approach.

The occurrence of the severe mixed atypical-melancholic MDD subtype in half of all PwMS is in parallel with earlier work on Pw/oMS showing that this subtype is common. Moreover, these studies found more comorbid disorders, higher depression severity, and a female preponderance of this MDD subtype [33,34,44]. Evidence regarding the high depression severity of this MDD subtype was reflected in its definition requiring the criteria of two different MDD subtypes, and by the fact, that it was clearly distinguishable from a MDD subtype with moderate severity in the data-driven approach. Such severity differences of MDD subtypes are consistent with previous studies demonstrating that apart from symptom patterns, also severity contributes to explain the heterogeneity of MDD [e.g., 45, 52, 60, 61].

The mixed atypical-melancholic MDD subtype was particularly characterized by a large number of somatic depression symptoms. In fact, this MDD subtype showed a remarkably high overlap with inherent features of the MS disease, such as 'psychomotor retardation', 'sleep disturbances', and 'leaden paralysis'. Accordingly, one might assume that the mixed atypical-melancholic MDD subtype mainly reflects a higher MS-inherent disability. However, this was not indicated in our results among PwMS as the EDSS proxy measure [62], time since MS diagnosis and total number of relapses did not differ between the severe and moderate MDD subtypes. Considering the high probability of somatic depression symptoms in the mixed atypical-melancholic MDD subtype, we found that the screening instruments commonly applied for PwMS were somewhat limited due to the exclusion of somatic depression symptoms as in the BDI-FS [5]. We do not question the appropriateness of the BDI-FS as a screening instrument for PwMS, it is simply less sensitive with respect to this particular MDD subtype in our study despite the high subjective burden and high probabilities for the main, non-somatic MDD criteria and 'suicidality' of these persons. Consequently, an accurate depression diagnosis might present a particular challenge within PwMS with the mixed atypical-melancholic MDD subtype bearing the risk of false negatives in clinical practice. The alternative explanation that PwMS more often develop mixed atypical-melancholic depression states merely due to the preponderance of women [44] is insufficient in this study, as the association remained significant even after adjustment for sex. In fact, this is a remarkable finding. We speculate that the high occurrence of the mixed atypical-melancholic MDD subtype in PwMS might be the result of, multicausal factors (such as inflammatory processes, reactive depression since the MS diagnosis and during the progression of the disease, collateral depression due to neuroinflammation /−degeneration) manifesting in a mixed rather than a pure MDD subtype. In any case, this MDD subtype, which not yet been categorized in DSM-5, deserves more attention in future research.

Contrary to our expectations, the atypical MDD subtype was neither more prevalent in PwMS nor replicated in the data-driven approach. However, as the pure MDD subtype derived by the DSM-5 criteria depicted the smallest group of depressives, it was probably statistically incorporated in the mixed atypical-melancholic MDD subtype in the three-class LCA solution of the data-driven approach. Therefore, our result distinguishing between pure and mixed MDD subtypes was in accordance with the study of Boeschoten et al. [29] not finding any difference of atypical depression clusters between PwMS and Pw/oMS, but at the level of depression symptoms.

4.2. Depression symptoms

In contrast to the lacking prevalence differences between PwMS and Pw/oMS relating to the atypical MDD subtype, differences were present in terms of atypical depression symptoms. Hence, this finding partially added weight to our hypothesis, as we also expected more atypical symptoms in PwMS compared to Pw/oMS. In our study, PwMS yielded a higher risk for the two somatic atypical depression symptoms 'leaden paralysis' and 'weight gain' and the symptom 'irritable/angry'. These symptoms were all especially pronounced in the mixed atypical-melancholic MDD subtype. Thus, our results corroborate previous findings by highlighting the relevance of somatic or neurovegetative depression symptoms in PwMS [22–25]; this held also after adjustment for sex, age, civil status and depression severity.

In contrast to Boeschoten et al. [29], 'leaden paralysis' thus reached the level of significance even after adjustment in the current study. In several other reports, information on 'leaden paralysis' was lacking, as depression symptoms were assessed by the BDI omitting this symptom [22–24,27,28]. Although 'leaden paralysis' has been defined as a core feature of atypical depression in several concepts [63], this symptom is particularly difficult to disentangle from MS-related fatigue and deserves more attention in this specific population. Concerning the higher occurrence of 'weight gain', the finding of a recent study [64] is interesting: the leading symptom for the association between depression and inflammatory and metabolic markers was 'increased appetite'. 'Increased appetite' correlates to 'weight gain'. However, it remains uncertain whether a comparable association with inflammation would occur for 'weight gain'. Again our finding differed from another study [29] where 'weight gain' was not associated with MS. This might result from the different time-frames considered for the assessment of the depression symptoms: past week interval in the latter study [29], past 12-months in the current study.

Apart from the two somatic atypical depression features, the symptom 'irritable/angry' was also more frequently present in depressed PwMS than in depressed Pw/oMS. This symptom does not belong to the regular MDD criteria. However, studies have emphasized that it characterizes depression in PwMS, which is possibly explainable by MS-related cerebral changes crucial for the maintenance of cognitive as well as emotional stability [12,25,65–68].

4.3. Limitations

This research is subject to several limitations. First, a limitation pertains to the general recall bias of self-reported data. Second, the Mini-SPIKE was applied as a self-rating questionnaire due to the general methodological approach of the SMSR. Thus, MDD prevalence in PwMS is expected to be underestimated in the SMSR since prevalence rates of mental disorders are likely lower if not assessed in face-to-face settings. Third, information on further psychopathological comorbidities, such as bipolar depression, has been omitted in this analysis despite its relevance in atypical depression [69]. Notably, the symptom 'irritable/angry' is relevant in bipolar disorders [70], but also within the premenstrual syndrome [71]. Finally, the cross-sectional design hinders causal conclusions concerning the temporal order of MDD, depression symptoms and MS.

4.4. Conclusions and outlook

The results of our study indicated that differences in MDD between PwMS and Pw/oMS resulted from the higher risk of PwMS for somatic atypical depression symptoms and the mixed atypical-melancholic MDD subtype. However, we found no differences between PwMS and Pw/oMS regarding the pure atypical MDD subtype. In fact, the somatic atypical depression symptoms were particularly pronounced in the mixed atypical-melancholic MDD subtype. As inflammation represents a core biological correlate of atypical depression [39] we thus cannot ascertain that MDD in PwMS may be linked to the MS-disease inherent inflammation. Even though immunological anomalies were judged to explain only a small proportion of the overall variance between MDD and MS [72], additional research on this topic is required. Important evidence was gained pertaining to the mixed atypical-melancholic MDD subtype: this group depicted a high overlap with MS features and thus represents a particular diagnostic challenge for health-care professionals. We cannot provide any etiopathogenetic explanations for the predominance of the mixed atypical-melancholic MDD subtype in PwMS nor clearly assign the overlapping features to either disease. However, we conclude that these features are obviously constitutive for this MDD subtype in PwMS and, moreover, crucially associated with high subjective burden. These research findings are important for the persons comorbidly affected by the two heterogeneous disorders MS and MDD. Last but not least, these results may provide the basis for advancing more specific pharmacological and psychological treatment strategies.

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Appendix A. Supplementary data

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